AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph starting on page 2, line 14 of the specification as filed with the following rewritten paragraph:

As set forth in U.S. Pat. No. 3,932,407 issued Jan. 13, 1976 and in Reissue patent No. Re. 31,617 Jun. 26, 1984 quinazoline derivative including ~~Aanagrelide~~ anagrelide can be prepared in a solid form for oral and/or parenteral use as blood platelet anti-aggregative agents and/or anti-hypertensive agents and/or bronchodilatator agents. However, the patent does not suggest that it would be desirable to avoid the first pass metabolism through the liver in order to reduce some of anagrelide side-effects when administered orally. The patent also does not suggest that it would be possible or desirable to prepare a transdermal formulation or to use the formulation for the treatment or prevention of thrombocythemia.

Please replace the paragraph starting on page 4, line 17 of the specification as filed with the following rewritten paragraph:

Figure 1 represents the mean plasma concentration-time profiles of anagrelide and Metabolite A after 1 mg ~~orally~~ administered orally (closed diamonds) and after dermal application of a saturated solution for 24 h (open squares).

Please replace the paragraph starting on page 13, line 4 of the specification as filed with the following rewritten paragraph:

In one embodiment, the thrombocythemia is associated with essential thrombocythemia (ET), chronic ~~myelogenous~~ myelogenous leukemia (CML), polycythemia vera (PV), agnogenic myeloid metaplasia (AMM) or sickle cell anemia(SCA).

Please replace the paragraph starting on page 18, line 23 of the specification as filed with the following rewritten paragraph:

In a further embodiment, anagrelide can be administered ~~trandermally~~ transdermally using a metered dose transdermal spray. In such system, the patient simply positions a unit comprising the active agent against the skin and activates the proper command to spray a small accurate volume of liquid comprising the active agent onto a defined area of skin. The liquid ~~Liquid~~ evaporates leaving an invisible water resistant deposit from which the drug is absorbed into the body. For example technology known as the Acrux™ technology can be used.

Please replace the paragraph starting on page 19, line 1 of the specification as filed with the following rewritten paragraph:

Percutaneous or transdermal delivery of pharmacologically active agents has become feasible in recent years largely due to vehicles ~~therefore~~ which allow increased permeation of said agents into the body surface to which applied. Such agents which may be useful for the preparation of transdermal formulation of this invention include, but are not necessarily limited to, dimethylsulfoxide (U.S. Pat. No. 3,551,554); various 1-substituted azacycloalkan-2-ones such as azone (U.S. Pat. Nos. 4,562,075, 4,405,616, 4,326,893 and 3,989,816); sugar esters in combination with sulfoxide or phosphine oxide (U.S. Pat. Nos. 4,130,667, 4,130,643, 4,046,886, 3,952,099, and 3,896,238); lower alkyl amides (U.S. Pat. No. 3,472,931); certain aliphatic sulfoxides (U.S. Pat. No. 3,903,256); a composition containing glycerol monooleate, ethanol and isopropyl myristate (U.S. Pat. No. 4,335,115); a binary mixture of 1-dodecylazacycloheptan-2-one and a compound selected from a diol or a second N-substituted azacycloalkyl-2-one (U.S. Pat. No. 4,557,934); and polyethylene glycol monolaurate (U.S. Pat. No. 4,568,343). U.S. Pat. Nos. 3,551,554, 4,562,075, 4,405,616, 4,326,893, 3,989,816, 4,130,667, 4,130,643, 4,046,886, 3,952,099, 3,896,238, 3,472,931, 3,903,256, 4,335,115, 4,557,934, and 4,568,343.

Please replace the paragraph starting on page 22, line 17 of the specification as filed with the following rewritten paragraph:

Preferred transdermal patch formulations include but are not limited to a patch formulation comprising an effective amount of anagrelide, azone, ethanol, water, optionally

propylene glycol and Klucel HF; anagrelide intimately distributed in a matrix; anagrelide and an acrylic adhesive; and [[an]] anagrelide, ethanol, and Klucel HF[[;]] as described herein.

Please replace the paragraph starting on page 30, line 20 of the specification as filed with the following rewritten paragraph:

EXAMPLE 8 Comparison between the Oral, ~~Intr-Venous~~ Intravenous and ~~Trandermal~~ Transdermal mode of ~~andimistration~~ Administration of Anagrelide in the Mini-Pig

Please replace the paragraph starting on page 30, line 23 of the specification as filed with the following rewritten paragraph:

The plasma level of anagrelide and metabolite A were measured in a mini-pig study following oral, ~~intra-venous~~ intravenous and transdermal administration of anagrelide.

Please replace the paragraph starting on page 34, line 1 of the specification as filed with the following rewritten paragraph:

Furthermore, data in patients suffering from myeloproliferative disease ~~has~~ have shown at steady state an even higher relative exposure to this metabolite compared to the parent drug ~~occurs~~ such that the ratio of metabolite to drug AUC ~~being~~ is close to 3:1. This is shown in the table below:

Please replace the paragraph starting on page 34, line 11 of the specification as filed with the following rewritten paragraph:

Earlier in vitro studies have already demonstrated the comparatively greater potency of metabolite A (40 fold) relative to anagrelide as an inhibitor of PDEIII. A study was conducted in a large group of dogs comparing metabolite A with the standard reference inotrope milrinone. A total of 12 animals have been used in this study which has shown metabolite A to be qualitatively like

milrinone in [[it]] its effects on the cardiovascular system but very considerably more potent. The essential conclusions from this work areas follows:

Please replace the paragraph starting on page 36, line 1 of the specification as filed with the following rewritten paragraph:

~~In order~~ This experiment was designed to confirm that lower continuous level exposure -- in contrast to the regular plasma higher peaks and troughs associated oral administration -- ~~were~~ was still effective in reducing blood platelets. It has been calculated that the maximum likely flux rate through human skin could give rise to a Cav of ~3-4 ng/ml. It was therefore important to demonstrate that at this level adequate reduction in megakaryocyte formation could be achieved.